THE USES OF 'BETAXAN'

Vitamin B_1

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(Vitamin B_1)

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Introduction

THE major problems of modern nutrition, both in health and disease, centre round the study of vitamins. This statement is not intended to suggest that the energy-supplying and tissue-building substances are neglected. No amount of vitamins will compensate for a quantitatively inadequate diet. But it is upon the vitamins that the utilisation of the grosser dietetic elements and the proper functioning of most, if not all, body tissues seems to depend. Our knowledge of vitamins A, C and D has progressed a surprising distance in the past twenty years. At last, vitamin B is catching up. This booklet is a summary of the present position and how it has been reached, together with an outline of the practical consequences of the conclusions reached.

HISTORY

Beri-beri is a disease occurring among the rice-eating populations of India, Japan, Malaya, the Dutch East Indies, the Philippine Islands and Louisiana. It has been endemic among the white wheaten flour eaters of Newfoundland and Labrador, and has broken out sporadically among soldiers and sailors, and in gaols.

As long ago as 1878, Baron Takaki, Director-General of the Japanese Naval Medical Service, demonstrated that polished rice was apparently an ætiological factor. He sent two battleships to sea, one crew having the routine polished rice diet, and the other additional diet of meat, vegetables, wheat and barley. In the first, beri-beri was rife, while in the second the only cases which occurred were found to be sailors who had refused the extra rations.

Nineteen years later, Dr. Christiaan Eijkmann, working in the Dutch East Indies, observed that fowls fed on polished rice developed convulsions, a spastic neck rigidity, and opisthotonos—a condition he termed polyneuritis gallinarum. Rice polishings added to the diet would prevent its onset, or give marked improvement in the established disease within a few hours. Applying his results to man, he studied over a quarter of a million individuals in Dutch East Indian prisons, where, thanks to local customs, various methods of preparing rice prevailed. His results were as follows : With unpolished rice, the incidence of beri-beri was 0·01 per cent. ; with a mixture of polished and unpolished rice, the incidence was 4·16 per cent. ; while with polished rice only, it was 39 per cent. It fell to Eijkmann's successor, Gerrit Gryns (1901),to show that it was not a toxin in the polished rice, but lack of the discarded cortex which caused the disease. As a result, rice-husk extracts became the standard treatment for beri-beri, and in 1914 the Philippine Government authorised

their free distribution to nursing mothers and infants in cases of infantile beri-beri—with excellent results.

In 1911, Funk, a Polish biochemist at the Lister Institute, obtained from rice husks a crystalline fraction capable of curing polyneuritis gallinarum in doses of 20 mgm. He grouped together beri-beri, scurvy, rickets and pellagra as deficiency diseases, and coined the term 'vitamine' for the unknown nutritional prophylactic factors.

Meanwhile, McCollum, studying nutritional factors in farm stock, discovered two food factors necessary for growth—the fat soluble vitamin A, and the water soluble vitamin B. The distribution of the latter suggested that it might be identical with the anti-beri-beri factor, but in 1919 H. H. Mitchell demonstrated that vitamin B was not a single entity. It contained a heat-labile,*growth-promoting, anti-polyneuritis substance, and a heat-stable, anti-rat-dermatitis substance. This second substance Goldberger (1926) showed would cure human pellagra, and 'black tongue' in dogs. Whereas the heat-labile substance has proved to be a single simple entity (B_1), the heat-stable substance has been fractionated into five or more entities. These are :—

VITAMIN B_2.	(Vitamin G) ; related to the yellow pigment lactoflavine ; growth-promoting in the rat.
VITAMIN B_3.	Weight-maintaining in pigeons and fowls.
VITAMIN B_4.	Probably prevents muscular weakness and spasticity in rats.
VITAMIN B_5.	Like B_3, but even less thermolabile. (Vitamins B_3 and B_5 may include the chicken anti-pellagra factor.)
VITAMIN B_6.	Anti-rat-dermatitis factor.
P.P. FACTOR ; (ANTI-PELLAGRA FACTOR).	Prevents human pellagra, and may prevent chicken pellagra and 'black tongue' in dogs.

* It is destroyed by *high* temperatures.

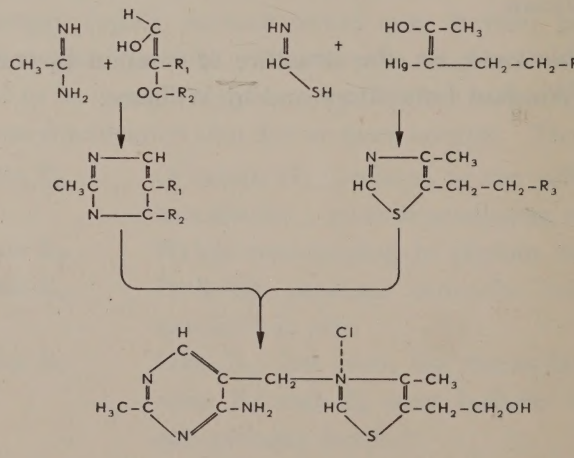
In 1927, Jansen and Donath, working in Eijkmann's Batavian laboratory, isolated from rice polishings extremely small quantities of a highly active crystalline hydrochloride, which Windaus in Göttingen subsequently showed contained sulphur. In 1931, the Göttingen Chemistry Laboratory, working in collaboration with the Bayer research department at Elberfield, isolated the same active principle from yeast. The supply of adequate quantities of the pure crystalline vitamin enabled detailed studies of its structure to be undertaken. The correct formula was established, and soon afterwards the anti-neuritic vitamin was prepared synthetically, in 1936, for the first time by Andersag and Westphal in the Bayer research laboratories. The synthetic vitamin B_1, manufactured in the Bayer laboratories, proved to be in every way identical, chemically and pharmacologically, with the anti-neuritic vitamin obtained in pure crystalline form from natural products. It was introduced commercially under the name Betaxan.

Much valuable work on the structure of vitamin B_1 was also done by the Windaus Laboratory and by Williams.

CHEMICAL AND PHYSICAL PROPERTIES

Vitamin B_1 is a hydrochloride, a white crystalline solid having the form of monoclinic plates. It is readily soluble in water, but it is insoluble in fats or oils. Its aqueous solution is acid to litmus and optically inactive. Its melting point is 246—7°C. It resists the action of weak acids, but is destroyed by alkalies. In the dry form, it will withstand heating, even in contact with air, to 100°. for 24 hours. In neutral or acid solution, it will withstand 100°. for several hours, but is fairly rapidly destroyed over 120°.

Chemically, it is a combination of a pyrimidine base and a thiazol ring, as a hydrochloride. The diagram below shows the chemistry of its synthesis :



(Vitamin B_1)

ASSAY OF STANDARDISATION

In the case of vitamins A and C, relatively simple methods of chemical estimation have been devised in the last few years. Unfortunately, chemical methods of estimating vitamin B_1 demand either a high degree of purity, or a strong concentration. Much is to be hoped from Jansen's thiochrome method, but for the present the activity of Vitamin B_1 still has to be measured *biologically*.

In 1931, the Vitamin Standardisation Committee of the League of Nations adopted as a standard for comparative purposes a concentrate of B_1 prepared by adsorption on Fuller's Earth. Ten milligrammes of this adsorption product constituted one international unit (I.U.). The Medical Research Council and the Lister Institute, at the request of the 1934 meeting of the Vitamin Standardisation Committee, have organised a large scale test of the synthetic vitamin B_1 hydrochloride against the international standard. As a result of 31 comparative experiments in 22 different laboratories, it was found, on an average, that

> 1 I.U. (10 mgm. of the adsorption product) is approximately equivalent to 3 γ (3 micrograms) of synthetic crystalline vitamin B_1, or
> 1 mgm. of crystalline vitamin B_1 is approximately equivalent to 333 I.U.

In view of the fact that many workers, both clinical and laboratory have come to think in terms of international units, the Committee feel that to abandon immediately the unit in favour of measures of the pure chemical substance would reintroduce confusion. They consider that the new definition of the international standard in terms of the pure substance will make an ultimate transition easier.

As already shown above, it is obvious that only biological tests can be used to demonstrate the physiological effect of vitamin

B_1, since only such tests can demonstrate whether the vitamin B_1 present in a substrate is in addition physiologically active. From the biologists's point of view the fact that vitamin B_1 is contained in the diet is not in itself sufficient, what must be established is that it can be absorbed and utilised. No chemical method can demonstrate the process of absorption and utilisation but only a biological method—i.e., comparison of the activity of an unknown product with that of a known standard preparation, namely, the international standard (=pure crystalline vitamin B_1 hydrochloride).

Some of the best known biological methods of comparative standardisation are, for interest, given below :—

1. *The pigeon curative test.*
A curative test requires fewer animals, less material and less time than a test based on maintenance of health or weight. Pigeons are fed on a B_1-free diet until classical polyneuritis with head retraction has developed. Varying doses of the test substance are given to separate birds, and the minimal dose needed to produce cure, which is often dramatic, is noted. The duration of the remission is recorded, and the concentration of vitamin B_1 is expressed in *pigeon day doses*—that is, the weight of the curative dose divided by the duration of the remission (Kennersley, Peters and Reader, 1928). One pigeon day dose is about 2·5 γ of pure vitamin B_1.

2. *The rat growth test.*
The unit used in this test is known as the *Sherman-Chase Unit*, and is defined as the daily dose of vitamin B_1 needed to produce a gain in weight of 3 gm. per week in a properly standardised and controlled rat over a period of four to eight weeks.

3. *The rat curative test.*
In principle, this is similar to the pigeon curative test. Young rats are reared from weaning on a B_1-free diet, and in 50 to 80 days develop typical polyneuritis. The test for polyneuritis is to pick up the rat by its tail and rotate it, whereupon convulsions should follow. The test doses are best given parenterally, as gastro-intestinal upset may reduce absorption.

4. *The rat bradycardia test.*
The electrocardiogram of a young rat, fed for three weeks on a B_1 deficient diet, shows a heart rate of about 350 per minute (normal

500 to 550). Vitamin B_1 will rapidly restore the rate to normal, and the increase in rate and duration of the increase are roughly proportional to the dose given. This is a simple, rapid and reliable test, and the animals may be used repeatedly (Drury, Harris and Maudsley, 1930).

5. *The mould growth test.*
The rate of growth of the mould *Phycomyces Blakesleeanus* is, within certain limits, directly proportional to the amount of vitamin B_1 present in its medium. This test is extremely sensitive and works with quantities as small as 0·01 γ (Schopfer and Jung, 1936),

The only chemical method worthy of mention is *Jansen's thiochrome method.* This depends upon the quantitative oxidation of vitamin B_1 to fluorescent thiochrome. This is estimated by comparison in a standardised photo-electric fluorometer.

PHYSIOLOGY

1. *Carbohydrate Metabolism.*

As long ago as 1914, Funk found that polyneuritis gallinarum was more rapidly produced the greater the carbohydrate intake of the birds. Subsequently it was discovered that vitamin B_1 lack produced severe upsets of carbohydrate metabolism, but it was for a long time disputed whether these might not be merely secondary effects of inanition. The work of Peters (1936) has, however, definitely shown that vitamin B_1 is a catalyst needed for the removal of one of the products of carbohydrate metabolism. Lactic and pyruvic acids are present in the avitaminotic pigeon's brain, and, *in vitro*, the addition of vitamin B_1 leads to a rapid increase in oxygen uptake as compared with normal brains. Further, Platt and Lee (1936) have demonstrated pyruvate in the blood and c.s.f. of beri-beri patients. Lohman and Schuster (1937) have shown that the pyrophosphate of vitamin B_1 acts as a co-carboxylase, and this may explain its ability to remove pyruvic acid.

2. *Nervous System.*

Nerve degeneration occurs in all types of animal suffering from B_1 lack. The polyneuritis is characterised by a degeneration of the myelin sheaths of the peripheral nerves. Degenerative changes in the central nervous system are less constant. It is interesting to note that Wolback (1937) could show no difference in the nerves of clinically cured pigeons and those allowed to die of polyneuritis. It would appear that the histological changes are not directly causative of the clinical findings.

3. *Cardiovascular System.*

Although B_1 lack in rats leads to bradycardia, Wenckebach (1928) and others have shown that in human beri-beri tachycardia is the rule. The usual findings in man are cardiac en-

largement with right-sided failure and œdema. How far this œdema is due to cardiac failure and how far to inanition and fall in serum protein is not known. A reduced serum protein has, however, frequently been found.

4. *Gastro-intestinal System.*

Anorexia resulting from B_1 lack is a very definite manifestation, and when the lack is remedied, the animal returns with relish to the food it previously rejected (Sherman, 1934). There is some disagreement over the alimentary lesions. There is almost certainly a hypotonia of the stomach and colon, less certainly a hypochlorhydria, and possibly a tendency to gastric erosion and ulceration (McCarrison, 1919). Pancreatic secretion appears to be diminished.

5. *Growth and weight maintenance.*

Vitamin B_1 is definitely necessary for growth, and weight and health maintenance, in rats and pigeons. Young rats need three to five times as much B_1 for growth as for maintenance of weight (Dann and Cowgill, 1934). During lactation increased supplies are also needed (Sure and Shilling, 1928) and the same seems to apply to infancy and childhood (Ross and Summerfeldt, 1935).

6. *Storage and excretion.*

The only considerable store, however, of vitamin B_1 appears to be the liver (2·6 I.U. per gm.), and this is quickly exhausted. The hog alone among animals has a large reserve. On a very high carbohydrate diet, the rat appears to be able to synthesise in its cæcum a vitamin B_1 substance. This is possibly due to a symbiotic micro-organism. Five to eight per cent. of vitamin B_1 ingested is quickly eliminated unchanged in the urine. The exact method of destruction of the rest in the tissues is not known. Vitamin B_1 has a definite diuretic effect—0·1 gm. per kilo

subcutaneously will double the water excretion in fasting rabbits. It is concluded (Harris, 1938) that the urinary excretion furnishes a useful guide to the state of nutrition of the subject with regard to vitamin B_1.

7. *Overdosage.*

The margin of safety for dosage with vitamin B_1 is enormous. The lethal doses by intravenous injection were 125 mgm. per kilo for mice, 250 mgm. per kilo for rats, 300 mgm. per kilo for rabbits, and 350 mgm. per kilo for dogs. The fatal doses for subcutaneous or oral administration were 6 to 40 times the intravenous (Molitor and Sampson, 1936). There appears to be no cumulative action. The minimum *toxic dose* is about 7,200 *times* the *therapeutic dose.*

DISTRIBUTION AND REQUIREMENTS

Vitamin B_1 is widely distributed and small amounts are found in almost all natural foodstuffs. The only considerable sources are, however, cereals, legumes, egg-yolk and pork, and, to a lesser extent, milk, liver, sweetbreads and nuts. Unfortunately, the modern methods of decorticating grains deprive us of our only rich supply. It must be remembered that, although relatively heat-stable, vitamin B_1 is water soluble, so that cooking methods inevitably drain off further quantities in addition to those removed by milling and husking. The following table (after Cowgill) gives the B_1 content of the more important foodstuffs, and it serves to illustrate the effects of preparation on the cereals :—

Vitamin B_1 contents in I.U. per oz.

Wheat germ	190	Peas, tinned	11
„ bran	56	Cow's liver	46
„ whole	28	Beef	7
„ flour	4	Pork	52
„ bread	3	Ham	30
Barley husked	26	Bacon	25
„ pearled	4	Eggs	28
Peanuts	56	Asparagus	20
Filberts	56	Parsnips	20
Hazelnuts	56	Prunes, dried	20
Beans, Kidney	50	Butter	11
Peas, dried	36	Milk	5
„ raw	21		

By way of contrast with these figures, 1 oz. of Betaxan is equivalent to over ten million I.U.'s, and one ampoule of Betaxan (2 mgm. of vitamin B_1) is equivalent to 666 I.U.'s.

So much for the available supplies. Turning now to the other side of the balance sheet, we must consider how much vitamin B_1 the body needs. Our knowledge of this subject rests largely on the careful work of Cowgill (1934). He has shown that the minimum daily requirement varies not only from person to person, but also from day to day in the same person, under different conditions of metabolism. The need for vitamin B_1 seems to depend on the body weight, the calorie requirement and the carbohydrate intake. The larger the bulk of carbohydrate in the diet, the greater the need for B_1.

The average European diet contains very little more than the bare minimum supply of vitamin B_1. The better working class diet averages 200 I.U. per day, while the richer classes take from 400 to 500 I.U. per day. A total of 200 I.U.s. per day is calculated as the *minimum* allowance for a man of 10 stone (Harris and Leong, 1936). Baker and Wright (1936) have seen beri-beri develop on diets probably containing as much as 300 I.U.s per day. It is of interest to observe that Baker, Wright and Drummond (1937) have calculated that even the very poor in England 100 years ago consumed much more vitamin B_1 than they do to-day.

It is apparent that there is much to be said for supplementing the daily diet with a generous allowance of vitamin B_1, especially among the poorer classes, so that they may be placed well above the minimum prophylactic allowance level.

GROSS LACK OF VITAMIN B_1—BERI-BERI

Beri-beri is the most severe clinical result of prolonged vitamin B_1 lack. The duration of B_1 lack required to produce it depends upon whether this is relative or absolute. Complete deprivation leads to symptoms in two or three months. A partial lack may exist for many months before the disease is manifest. The attack falls mainly upon three systems, the nervous, the cardio-vascular and the alimentary.

The earliest changes are anorexia, epigastric discomfort, constipation, muscular weaknesss, lack of energy and vague pains. Later, peripheral neuritis develops. Areas of numbness, together with weakness and heaviness, appear in the limbs. Severe localised paræsthesiae, aching, gnawing or burning, occur in the legs or arms. On examination, the deep reflexes are found to be diminished or lost, the muscle power is feeble, there are areas of anæsthesia and hyperæsthesia, and extreme tenderness on pressure over the nerve trunks. Foot and wrist-drop develop later, and even complete lower motor neurone pareses (Dry beri-beri).

As the disease progresses, cardio-vascular symptoms and signs appear. First are noticed palpitations and tachycardia, the heart becomes enlarged, an apical systolic murmur appears, œdema develops around the ankles and over the tibiae, the liver is congested and tender, and finally ascites, effusions, and generalised anasarca set in (Wet beri-beri).

Gastro-intestinal symptoms occur both early and late. Loss of appetite is a most common early sign. Glossitis frequently occurs—possibly due to lack of other elements in the vitamin B complex. Bowel atony and resulting constipation are usual.

Other changes occurring in beri-beri are a raised blood-sugar, a low serum protein, secondary anæmia, and mental depression sometimes amounting to a definite psychosis.

In infancy, the onset is more rapid and the clinical picture more acute. Generalised paroxysmal muscular spasms may lead to death in 24 hours (Hoobler, 1931).

Acute cases of beri-beri respond rapidly to full doses of vitamin B_1. Chronic cases are slower, and some irreversible damage may prohibit complete cure.

MILD DEGREES OF VITAMIN B_1 LACK

Although frank beri-beri is seldom seen outside the tropics, it is widely held that minor degrees of B_1 lack are common in temperate climates. Kühnau (1935) describes the clinical picture as consisting of lack of appetite, pains and paræsthesiae in the limbs, low blood-pressure, and a low body temperature. On a moderate degree of vitamin B_1 deficiency, 300 Japanese labourers were found to show physical impairment as soon as the diet was started, although classical beri-beri did not develop for three to four months (Fraser and Stanton, 1911, quoted by Eddy and Dalldorf, 1937).

Peters (1937) observes that " the statement commonly made, that because an individual eats a good mixed diet, he cannot be suffering from vitamin deficiency, is mere dogmatism . . . as a general symptom of vitamin lack, probably failure of appetite is the most important, and the most important vitamin in this connection is vitamin B_1." He advocates (1936) its clinical use in " conditions of loss of appetite with œdema, palpitations, and breathlessness, especially where there is defective removal of blood lactic acid after exercise, neuritic conditions and painful muscles."

Under certain special circumstances, mild degrees of B_1 lack are liable to become more pronounced :—

Infancy. The relatively great need for vitamin B_1 by the growing child has already been referred to. The child of a nursing mother, herself free from beri-beri, may develop the disease. Infants and children with poor appetites who fail to maintain growth-rate and general nutrition, are not infrequently suffering from vitamin B_1 lack, and rapidly improve when this deficiency is corrected. Morgan and Barry (1930), for example, found that in a group of poorly nourished infants the weight gain was three times as great after wheat germ was added to their diets as before.

Pregnancy and Lactation. Animal experiments demonstrate that, compared with the normal animal, 3 to 5 times as much vitamin

B_1 is needed by the pregnant female to produce and raise a litter. Clinical experience bears out these results in women. Sure (1928), has estimated that as much as 60 per cent. of the daily intake of vitamin B_1 is lost in the milk. The most serious manifestation of vitamin B_1 lack in pregnancy is polyneuritis, which is discussed below. However, other upsets are probably also associated ætiologically. Balfour (1931) found a marked lack of this vitamin in the diets of women who had produced premature infants.

Strauss and McDonald (1935) were able not only to cure polyneuritis of pregnancy with generous doses of yeast, but also *hyperemesis gravidarum*, a disease in which vitamin B_1 lack may prove to be a partial ætiological factor. Joachimovitz (1936) also relieved hyperemesis by vitamin B_1 administration. In such cases, parenteral administration is preferable. Widenbauer (1936) describes a case in which hyperemesis combined with an unsuitable diet produced severe B_1 hypovitaminosis, as evidenced by exhaustion, dyspnœa, præcordial pain and paræsthesiae. These symptoms rapidly vanished on treatment with intramuscular injections of Betaxan. *Special diets* are often gravely deficient in vitamin B_1, and call for an adequate supplement of some preparation of the vitamin. In particular, this applies to routine diets for *gastric and duodenal ulcer*, the *high carbohydrate* diets sometimes employed in nephritis, and reducing diets for *obesity*.

Increase in metabolism. In febrile conditions, there is an absolute increase in vitamin B_1 requirement. The same appears to hold good for increased metabolism due to thyrotoxicosis. Sure and Buchanan (1937) found that crystalline vitamin B_1 prevented symptoms of thyrotoxicosis in rats fed on large doses of thyroxin. Clinical studies by Sturm (1935), Lohr (1936), and Means, Hertz and Lerman (1937) have confirmed the favourable effect of vitamin B_1 in hyperthyroidism.

VITAMIN B_1 AND NEURITIS

That a connection existed between vitamin B_1 lack and the peripheral neuritis seen in pregnancy and alcoholism has been suspected for many years. The first big clinical investigation was that of Vorhaus, Williams and Waterman (1935). One hundred mixed cases of peripheral neuritis (41 metabolic—including alcoholic, 20 infections, 22 localised, 11 anæmic, 3 pregnancy cases, and 3 various) were treated with 10 mgm. of crystalline vitamin daily. As a result 44 per cent. were cured and another 48 per cent. improved. Stevenson (1938) has also shown that vitamin B_1 provides a factor often necessary for the efficient clearing up of neuritis and suggests that without it the condition would probably remain chronic.

Alcoholic Neuritis has long been regarded as a toxic phenomenon. Jolliffe, Colbert and Joffe (1936), showed that, in every case in their series, the vitamin-calorie ratio— if the calorie value of the ingested alcohol was included—was below Cowgill's minimum protective figure. Of 28 cases treated by Jolliffe and Colbert (1936), those on barely adequate B_1 dosage did not improve, those on twice the minimum dosage improved slowly, while those on four times the minimum improved rapidly. Two refractory cases showed dramatic improvement in two or three days on intravenous injection of crystalline B_1. Knee jerks returned, foot drop vanished, and sensory symptoms were relieved. It does not even appear necessary to restrict the alcohol intake in these cases. Strauss (1935) reports improvement in every case following B_1 therapy in a group of patients whose daily ration of whisky varied from one pint to one quart. Thompson (1937) suggests that the achlorhydria of chronic alcoholism is an important causative factor, inasmuch as vitamin B_1 is known to be rapidly destroyed in alkaline media. For this reason, the parenteral route of administration is advised.

Pregnancy polyneuritis also responds rapidly to vitamin B_1 therapy. Ogata (1920) observed that beri-beri often came on during pregnancy, but it was left to Strauss and McDonald (1933) to show that pregnancy polyneuritis due to hyperemesis and/or inadequate diet was quickly relieved by vitamin B. The symptoms are numbness and tingling, deep gnawing pains, weakness, tenderness, and sometimes loss of deep reflexes. Vorhaus, Williams and Waterman (1935), confirmed the rapid effects of using crystalline vitamin B_1, and Theobald (1936), Stähler (1937) and Kann (1938), obtained similar results. Bingham (1936), advises the use of vitamin B_1 as a prophylactic measure in pregnancy.

Other varieties of neuritis. Although logically speaking there is no reason why vitamin B_1 therapy should be of any value in cases of peripheral neuritis not definitely associated with vitamin B_1 lack, nevertheless numerous reports of its successful use in neuritic conditions continue to appear. It has been suggested that the neuritis due to various toxic agents is produced in the same way as that of alcohol, and success is claimed for Betaxan in *thallium neuritis* (Heimann, 1936) and *arsenical neuritis* (Gallowitsch, 1937). Kühnau (1937) has suggested that the neuritis of *lead poisoning* is associated with defective absorption of vitamin B_1, while Heimann (1937) puts forward a similar thesis to explain the neuritis of *diabetes*, *pellagra*, *carcinoma* and *starvation*. Ruschke (1936) has had success with Betaxan in *nicotine neuritis*. The same worker and Schwochow (1937) found Betaxan to be effective in *post-influenzal neuritis*.

Successful claims are also made for vitamin B_1 in cases of neuritis involving individual nerves. Von Lobenstein (1936) treated successfully with Betaxan two cases of *brachial plexus neuritis*, two of *radial neuritis*, and two of partial paralysis of the *facial* nerve. Ebermaier (1937) cites a case of *ulnar neuritis* cured by five

injections of Betaxan. Hesse (1936), using Betaxan, treated successfully four cases of *anterior crural neuritis*. Fetscher (1936) describes two cases of *occupational neuritis* treated with Betaxan. Both were musicians, and both were able to resume work. *Traumatic neuritis* following parturition was greatly improved by Betaxan (Gaehtgens, 1936), while Schwochow (1937) obtained a similar result.

Benefit in cases of *sciatica* is recorded by many workers (Ruschke, 1936 ; Schwochow, 1937 ; Fetscher, 1936 ; von Lobenstein, 1936 ; and Haberkamp, 1937). One of Ruschke's patients was free from pain after six injections of Betaxan, while a case of Fetscher's was free from pain after three injections, and had recovered normal movement by the sixth.

Good results are also described with Betaxan in *post-diphtheritic paralyses* (Neumann, 1935 ; Bennholdt-Thomsen, 1936 ; and Knapp, 1937) ; *trigeminal neuralgia* (Bohm, 1936) ; *intercostal neuralgia* (Ruschke, 1936) ; the nerve pains of *tabes dorsalis* (Neuman, 1935) ; and *retrobulbar neuritis* (Shastid, 1929). In cases of *subacute combined degeneration*, which fail to respond to liver, Betaxan injections have been used with success (Lasch, 1936 ; Müller-Deham, 1937, etc.).

VITAMIN B_1 AND THE HEART AND ALIMENTARY TRACT

Cardiac Conditions. The true beri-beri heart is in a severe condition —cardiac enlargement and congestive failure. For it, massive B_1 therapy is required, and large doses may give dramatic relief in two to three hours (Hashimoto, 1937). Weiss and Wilkins (1936, 1937) have studied 35 cases of nutritional deficiency showing cardiac dysfunction, and 30 of these made a complete recovery on vitamin B_1 therapy. Jones and Sure (1937) have reported a similar series of 18 cases of cardiac insufficiency successfully treated with B_1 concentrates and a high vitamin diet. Carmalt-Jones (1932) has obtained promising results in the treatment of oedema, for example, when associated with pernicious anæmia, with a vitamin B_1 preparation. Cardiac cases of nutritional origin are probably rare, but the possibility of a dietetic insufficiency should always be borne in mind in unexplained congestive failure.

Alimentary Tract. The existence of a syndrome of chronic vitamin B_1 lack, with alimentary symptoms preponderating, is suggested by many workers. Stepp (1936), describes as the typical picture anorexia, anacidity, atony of stomach and intestines, and a tendency towards inflammatory conditions of the bowel. Hartsock (1936) and Simpson (1936) give similar lists of symptoms. The presence of anacidity is disputed by Alvarez (1936) and Kitamura and Shimazono (1912). Stepp, Kühnau and Schroeder (1937) believe that a multiple B complex deficiency exists in most cases of spastic colon and ulcerative colitis, which have previously been described as due to B_1 lack only.

According to Stevenson (1938) therapy with vitamin B_1 is useful in the treatment of general debility, loss of appetite, or impaired bowel action. Vorhaus, Williams and Waterman (1935) suc-

ceeded in producing improvement in eight cases of gastro-intestinal hypotonia with 10 mgm. oral doses of pure vitamin B_1. Brown (1936), claims benefit from large doses of the vitamin in ulcerative colitis. Peters (1936) states as his considered opinion that, in every case of failure of appetite, the vitamin B_1 content of the diet should be considered with a view to correcting any inadequacy. He advises the use of a concentrated preparation, as the natural sources of the vitamin are too dilute for adequate therapy.

These are some of the published opinions on the possibilities of vitamin B_1 therapy in this group of diseases. It will suffice to add that in atonic bowel conditions, and in inflammatory upsets, where B_1 lack is suspected, the parenteral route of administration is to be advised to preclude faulty absorption.

X-Ray Sickness. In cases of X-ray sickness followed by vomiting, Martin and Moursund (1938), recommend Betaxan on the basis of their experimental and clinical experience previous to the use of X-rays.

INDICATIONS AND DOSAGE

INDICATIONS. In the **first** group of diseases, where a deficiency is known to be present, are :

Beri-beri,

Alcoholic polyneuritis, and

Polyneuritis of pregnancy.

In the **second** group, where a deficiency may be present and where empirical treatment has given good results, are :

Toxic polyneuritis.

Neuritis of single nerves—e.g., sciatic, brachial, crural or optic neuritis.

Neuralgia—intercostal, trigeminal and other forms.

Tabes dorsalis (pains), and subacute combined degeneration.

Hyperemesis gravidarum.

Loss of appetite, bowel atony, and constipation.

Ulcerative colitis.

Unexplained cardiac failure and œdema.

In the **third** group, where the diet is definitely deficient in B_1 in relation to metabolic needs, are :

Pregnancy, lactation and infancy.

Febrile diseases.

Hyperthyroidism.

Gastric Ulcer diets.

High carbohydrate diets.

Diets for obesity.

PROPHYLAXIS. In view of the narrow margin between prophylactic needs and the supplies in the diet of a large part of the population, a routine supplementary dose of vitamin B_1 has much to commend it. It might well be added to one of the bland daily foodstuffs. A prophylactic daily dose during pregnancy, lactation and infancy seems especially desirable.

DOSAGE. Betaxan can be given by mouth or parenterally. In view of the possibility of failure of absorption by the alimentary route intramuscular injection is advised in all cases with alimentary upset.

The minimum daily maintenance dose is 333 I.U.'s (equivalent to 1 mgm. of Betaxan). A safe *therapeutic* and *prophylactic dose* is 1-3 mgm. of pure vitamin B_1 three times a day by mouth (one tablet of Betaxan contains 1 mgm. of pure vitamin B_1). The usual intramuscular dose is 2-4 mgm. per day. (1 ampoule of Betaxan contains 2 mgm. of the pure vitamin.) There is no danger of cumulative action.

Massive doses of 10 mgm. per day, either by mouth or parenterally have been advised by some physicians, and are particularly indicated in acute severe B_1 lack. Special " forte " ampoules of Betaxan containing 10 mgm. of pure vitamin B_1 in 1 c.c. are available for these cases.

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